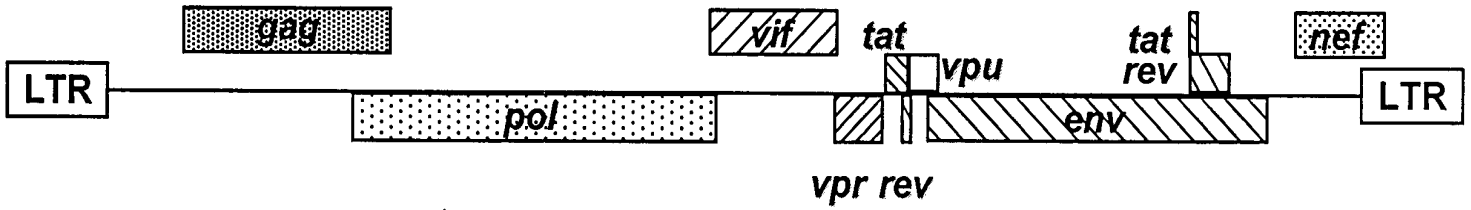
Resistance Test Vector

HIV-1



Resistance Test Vector

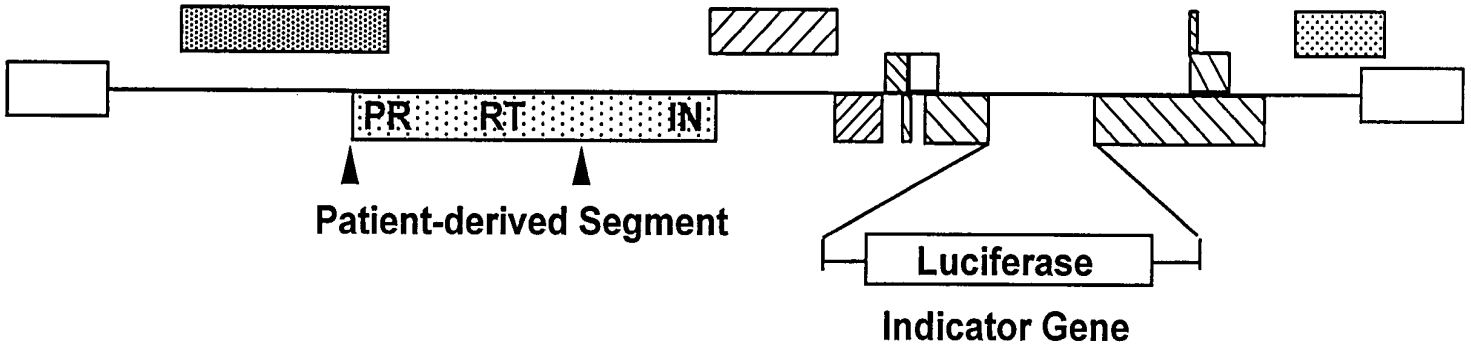


Fig. 1

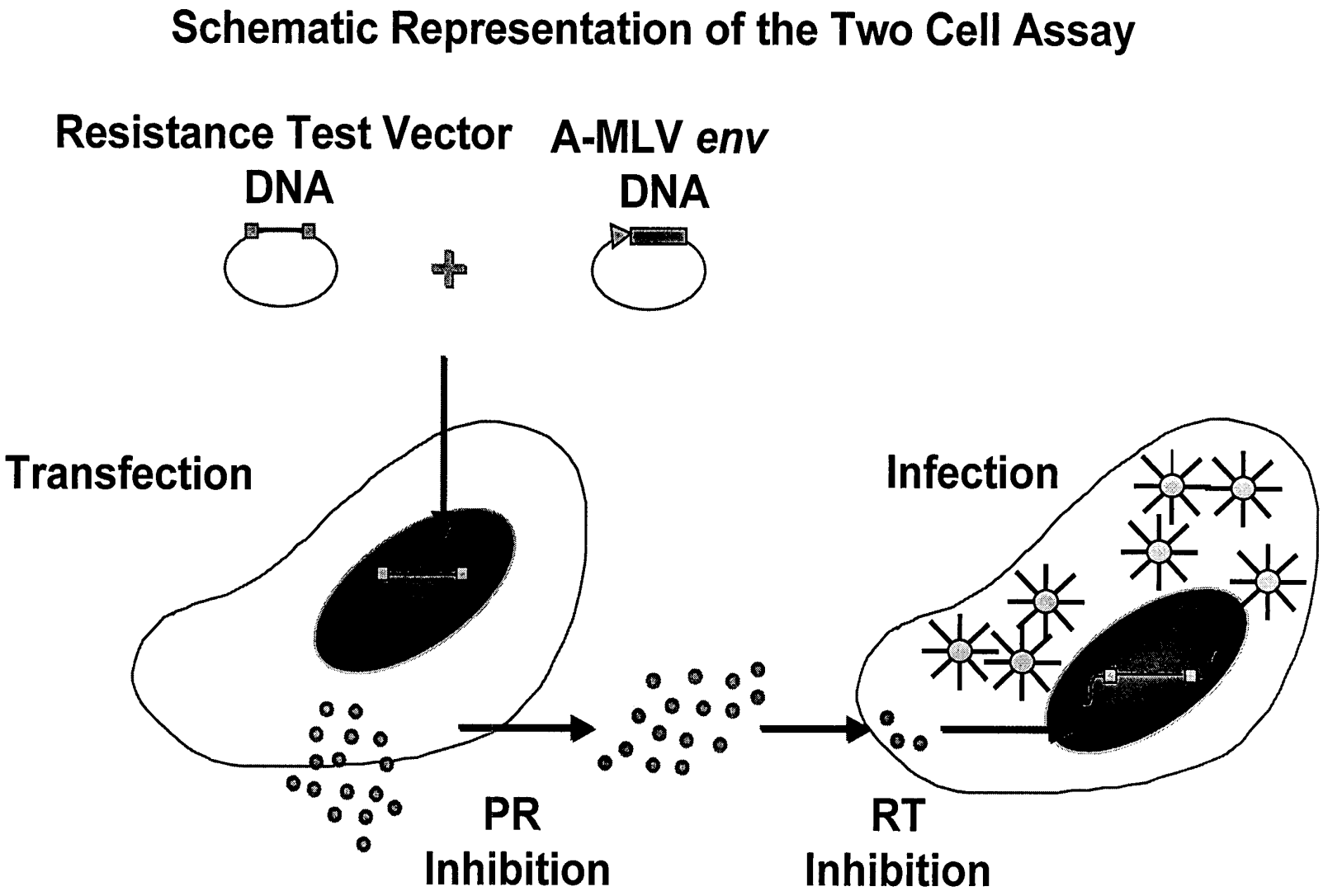

Schematic Representation of the Two Cell Assay
Resistance Test Vector DNA
A-MLV env DNA
Transfection
Infection
PR Inhibition
RT Inhibition

Fig. 2

Examples of Phenotypic Drug Susceptibility Profiles

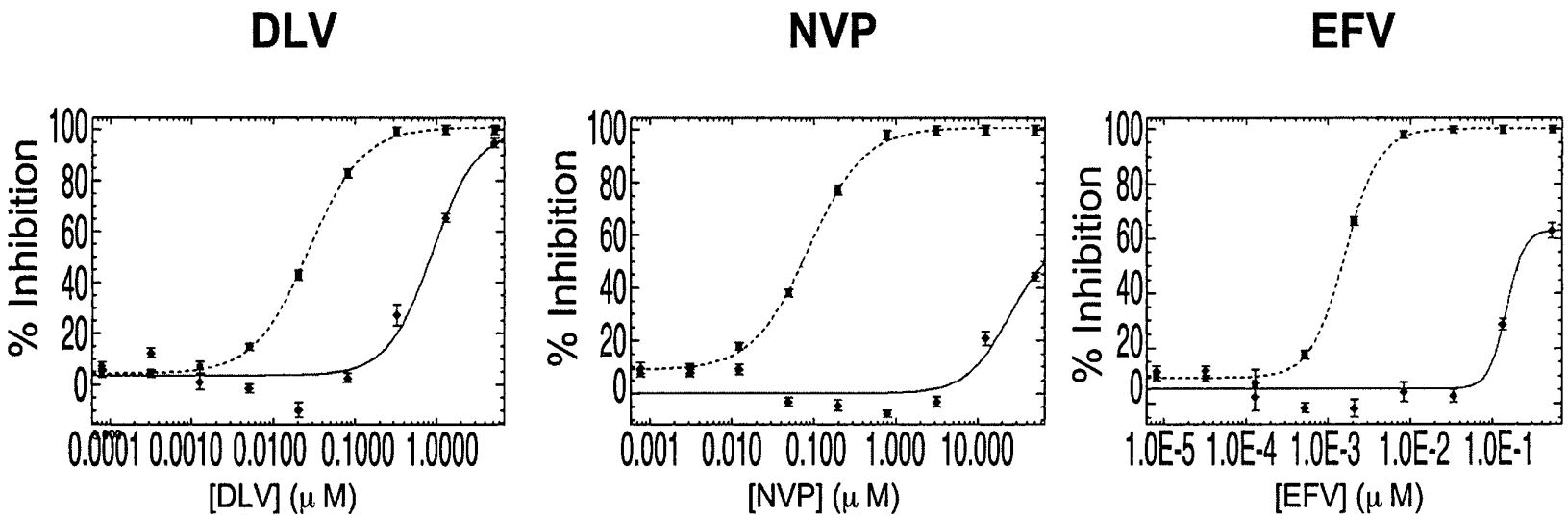


Fig. 3

Examples of Viruses exhibiting drug-dependent stimulation of viral replication

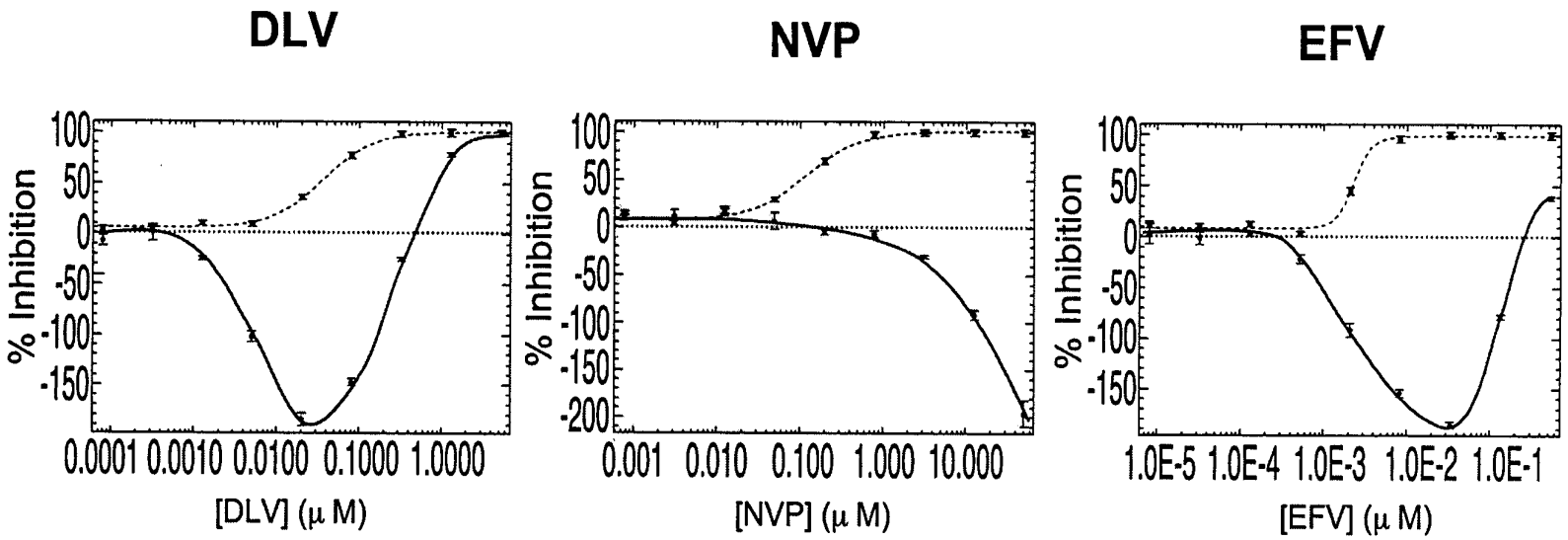


Fig. 4

Table of patient viruses containing M230L mutations (example 3, 4, and 5)

ACCESSION #	Date of Draw	Mutations Observed in Reverse Transcriptase	DLV	EFV	NVP
ARG-014 (Example 3)					
98-773	11/18/97	M41L, L74I, M184V, L210W, R211K, T215Y, L228R, T296S	0.3	0.3	0.4
98-1046	1/13/98	M41L, L74I, Y181C, M184V, H198L, L210W, R211K, T215Y, L228R, M230L, T296S	>250	5.3	>600
98-887	3/17/98	M41L, L74I, Y181C, M184V, L210W, R211K, T215Y, L228R, M230L, T296S	160.9	6.7	>600
CCTG-2165 (Example 4)					
99-2-009089	11/10/99	K49R, Q102K, K122E, E169D, I178M, M184V, I195T, T200A, R211K, V245M, D250E, K275Q, V276I, R277K, T286A, P294T	0.9	0.2	1.1
00-2-010835	1/26/00	K49R, Q102K, K103N, K122E, E169D, I178M, M184V, I195T, T200A, R211K, M230L, V245M, D250E, K275Q, V276I, R277K, T286A, P294T	>250	269.7	>600
CCTG-1025 (Example 5)					
AA2919	3/30/99	D67D/N, D86E, Q102K, V118I, K122P, A158S, C162S, Q174H, D177E, R211K, F214L, T215Y, A272P, K275N, V276V/A/I/T, R277K, Q278H, K281R, T286A, V293I	0.4	0.5	0.7
00-2-012090	2/29/00	D67N, D86E, K101K/E, Q102K/R, K103K/N, V118I, K122P, A158S, C162S, Q174H/R, D177E, G190G/S, L210L/R/W, R211K, F214L, T215Y, H221H/Y, M230M/L, K238K/T, A272P/S, K275K/Q, V276V/A/I/T, R277K, Q278Q/H, K281K/R, T286A, V293I	144.0	>450	>600

Fig. 5

Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutants K103N and M230L

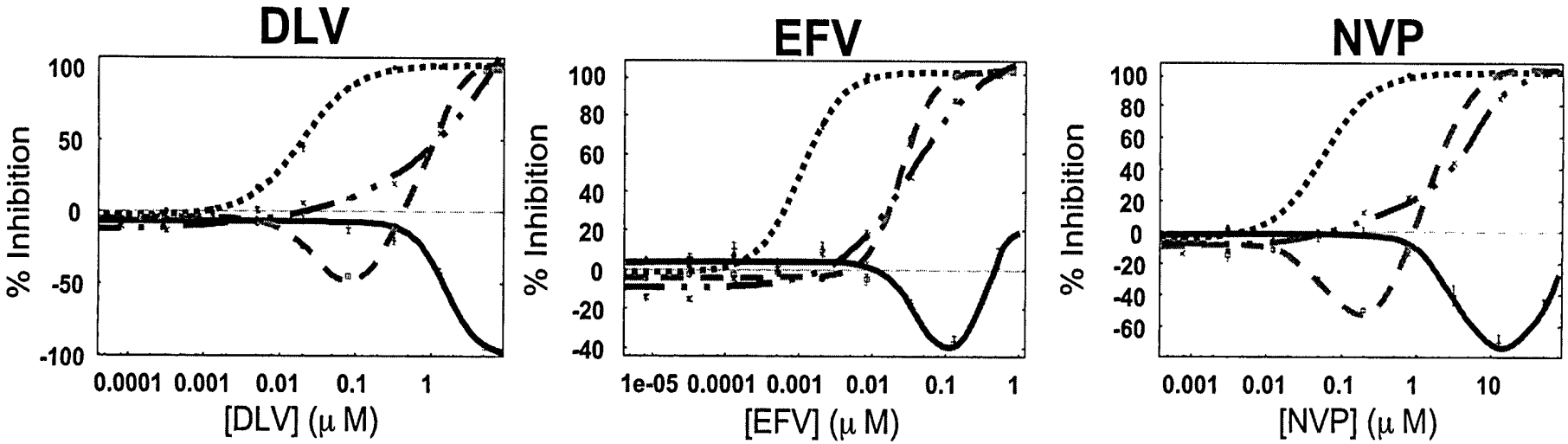


Fig. 6

Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutants Y181C and M230L

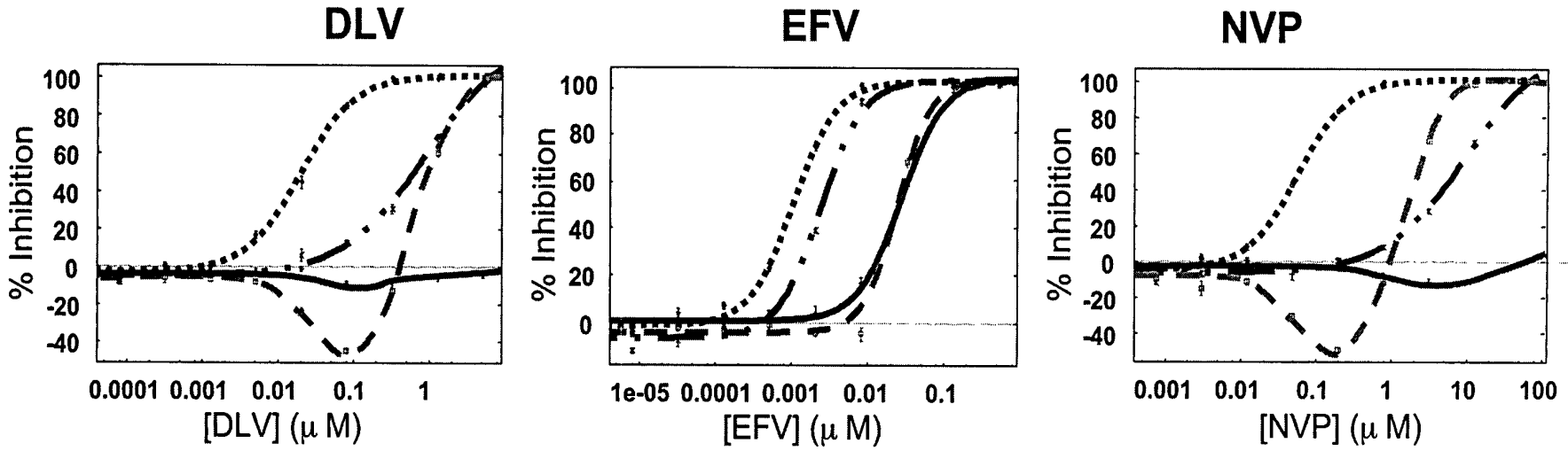
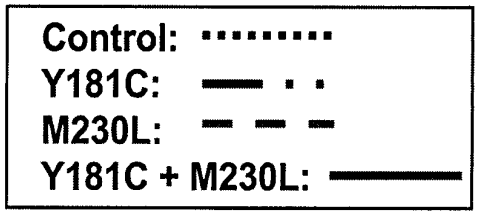


Fig. 7



Patient 11073, reverse mutagenesis of positions 241 and 277 (example 6)

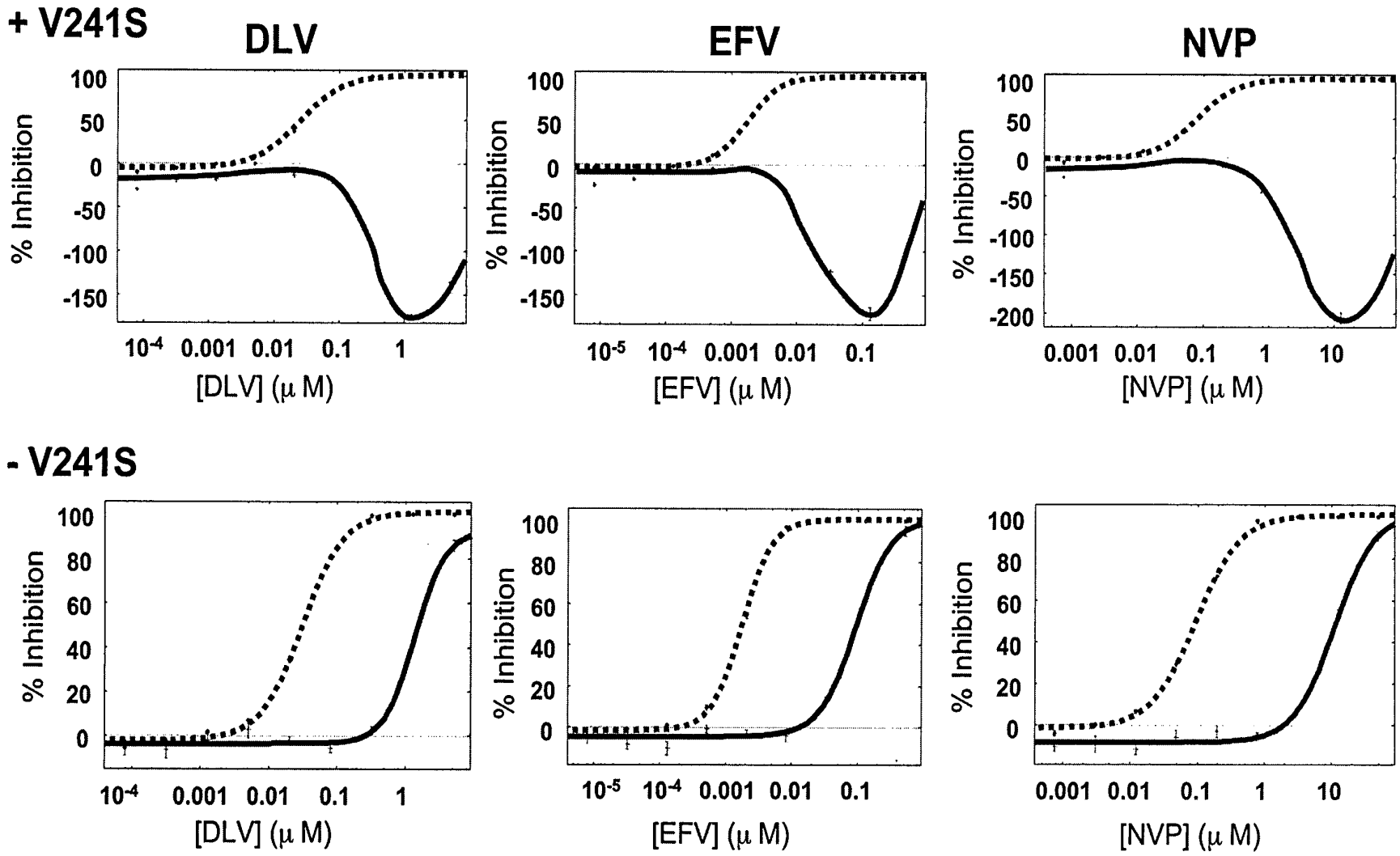


Fig. 8

Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutants V241S

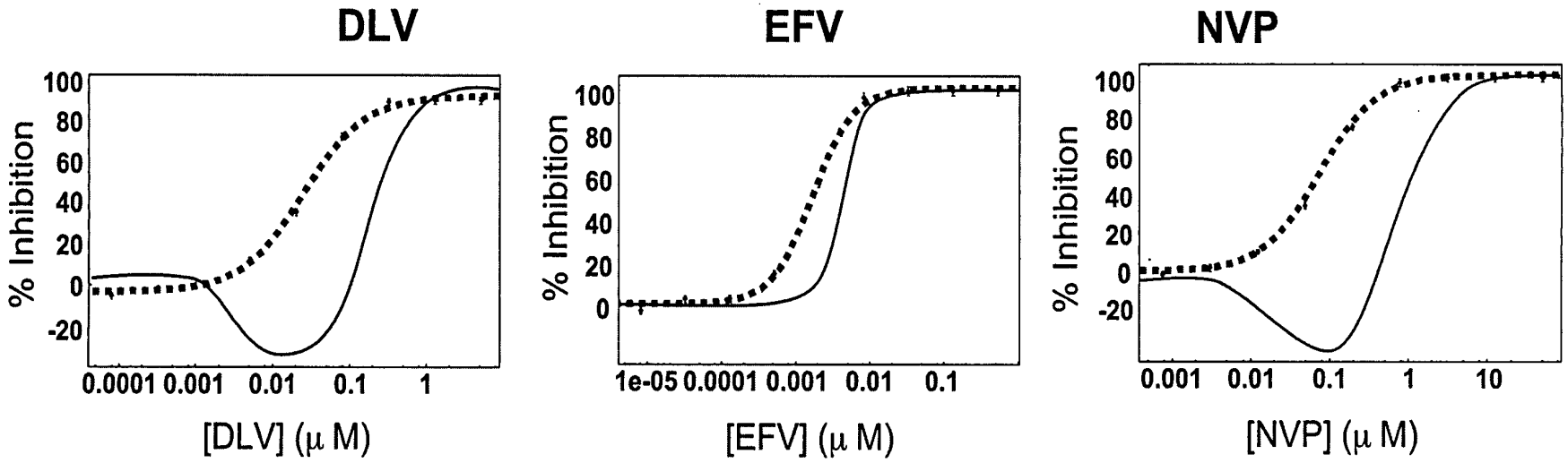


Fig. 9

Patient 014451, reduced susceptibility to NNRTI and drug dependent stimulation of viral replication associated with mutations at 101, 106 and 190 (example 7)

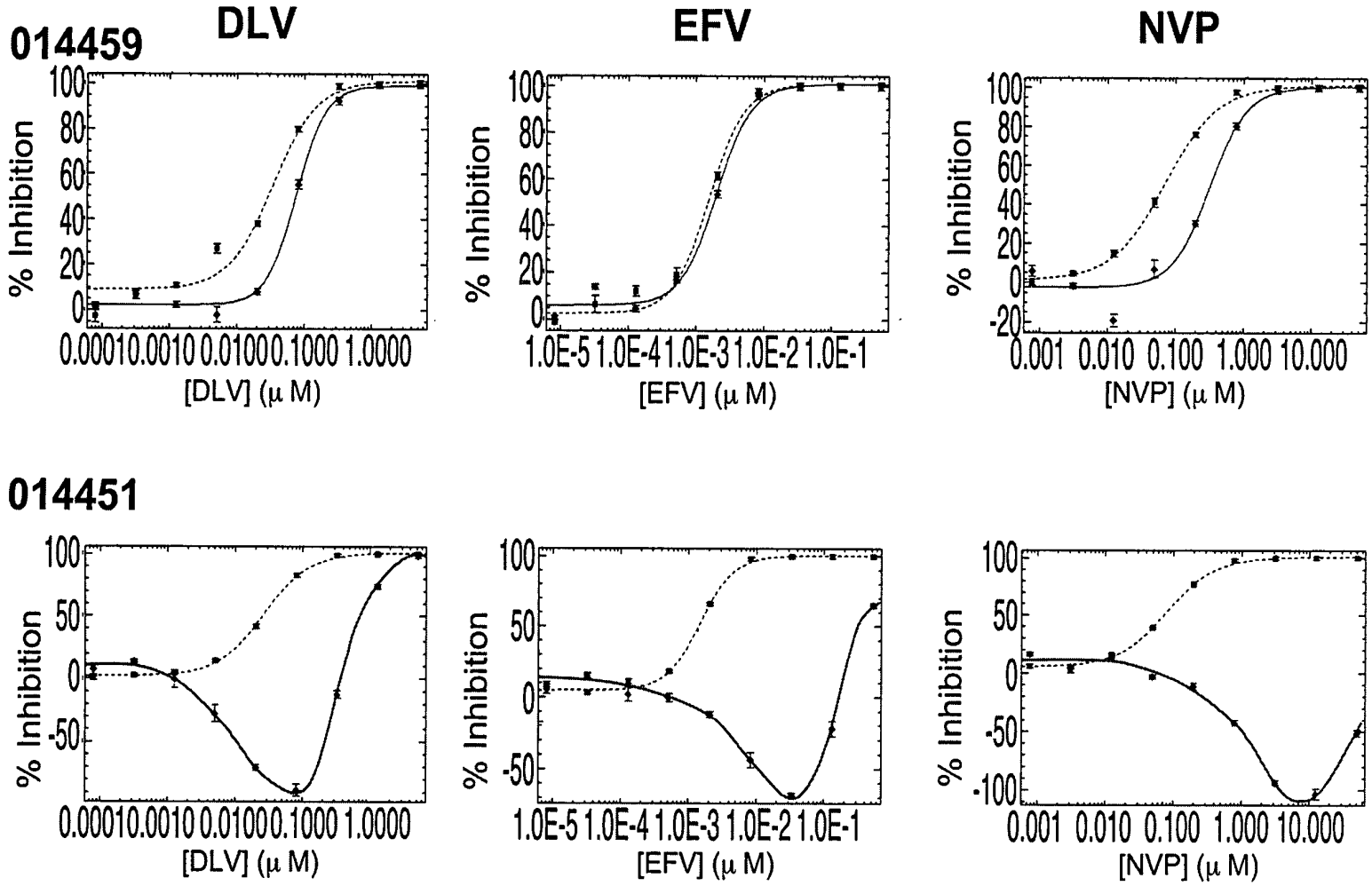


Fig. 10

Table of patient viruses containing mutations at amino acid 245 (examples 8 - 11)

Accession #	Mutations in Reverse Transcriptase	DLV		EFV		NVP	
		Fold Change	Stimulation	Fold Change	Stimulation	Fold Change	Stimulation
00-2-005738	D67N, K70R, R83K, A98G, Q102K, K122P, I135T, I142V, C162S, K173Q, I178L, Y181C, G196E, I202V, T215F, D218E, K219Q, V245E, A272P, R277K, V293I, E297Q	63.2	40%,	17.5	20%	>600	20%
00-2-011311	K43K/E, D67N, K70R, Q102K, K103N, K122E, I135I/M, C162S, Q174A/E, I178I/R, M184V, G190G/A, Q207E, H221H/Y, E224E/G, V245E, A272P, R277K, L283I, K287K/Q, V293I	>250	40%	>450	40%	>600	30%
00-2-10829	I31L, V35I, V90V/I, Q102K, K103N, K122E, C162S, G196E, R211K, F214F/L, T215Y, L228H, V245E, I270M, V276V/I, R277K, V292I, V293I, E297K	>250	100%	>450	80%	>600	100%
00-2-006782	Q102K, D123E, I135T, E138A, C162S, G196E, I202V, V245T, R277K, T286A, V293I, P294T, E297K	18.5	70%	5.2	25%	7.8	60%
00-1-012123	K20R, T39E, M41L, E44D, V60I, D67N, A98G, Q102K, K103N, V118I, K122E, I135T, I142V, C162S, K173Q, Y181C, G190A, G196E, I202V, L210Y, T215Y, H221Y, V245T, A272P, R277K, V293I, E297K	>250	80%	>450	70%	>600	0
00-1-014397-01	I31L, Q102K, K103N, D123E, C162S, K166R, D177E, R211K, T215F, L228R, V245T, A272G, R277K	>250	100%	>450	70%	>600	100%
00-1-013415	V35T, Q102K, K103N, K122E, D123N, I135T, C162S, D177E, T200A, Q207E, R211K, P225H, V245M, L264F, R277K, T290S	>250	30%	>450	20%	>600	20%

Fig. 11

Patient 010829: Effect of reversion of mutations at 245, 270, 277, 292, 293 and 297

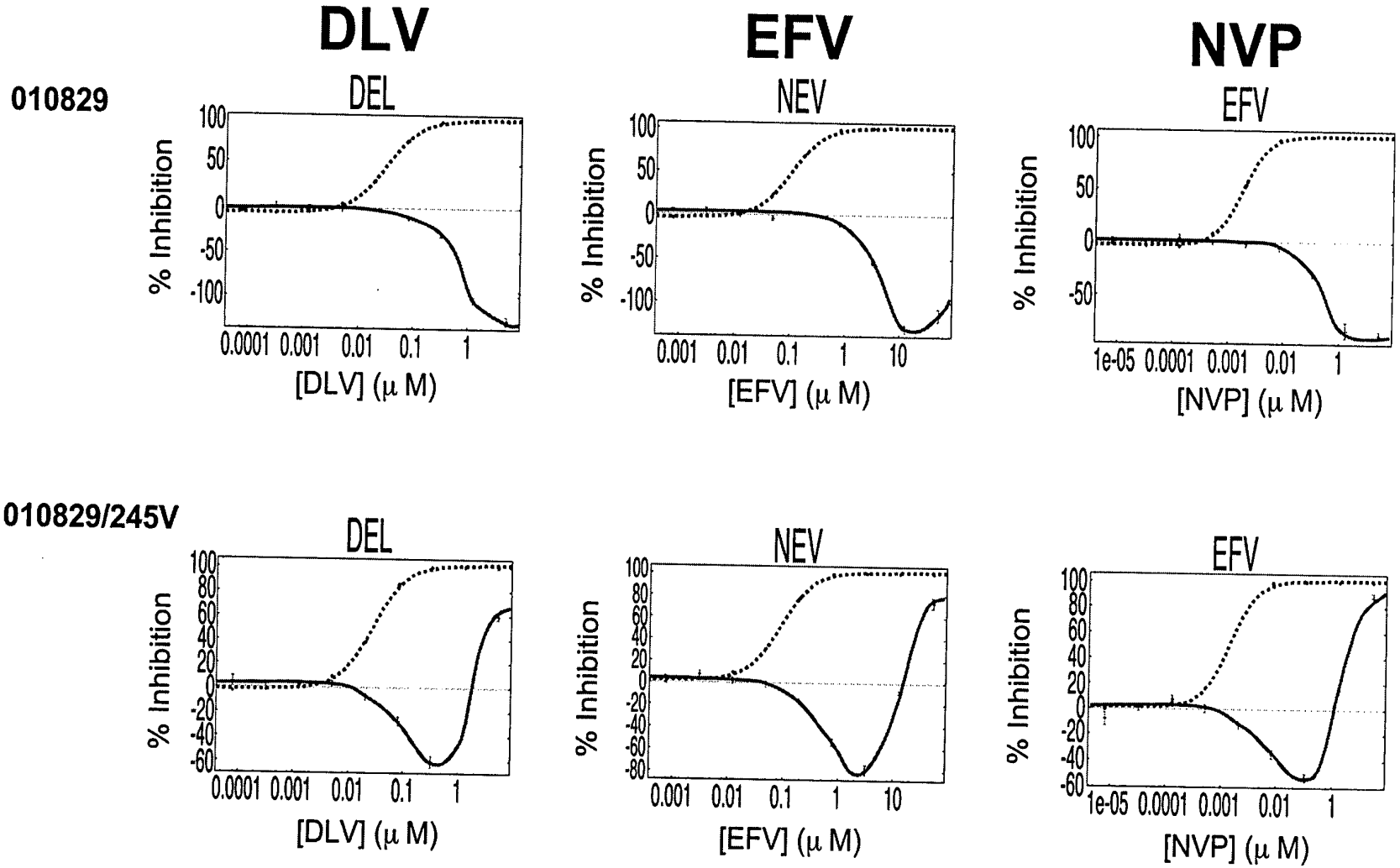
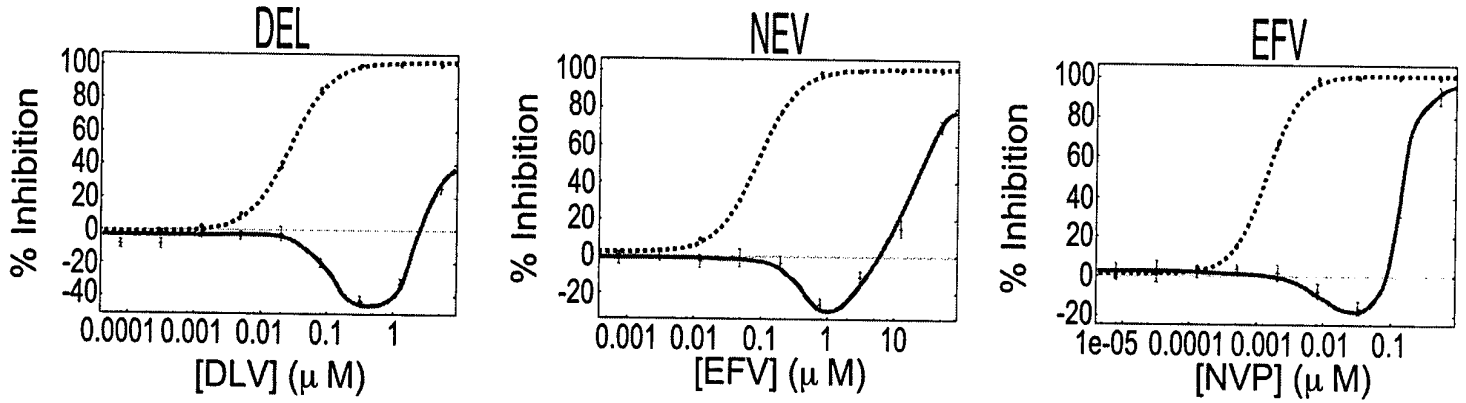


Fig. 12A

Patient 010829: Effect of reversion of mutations at 245, 270, 277, 292, 293 and 297, cont.

010829/270I



010829/245V/ 270I/277R/292V/ 293I/297E

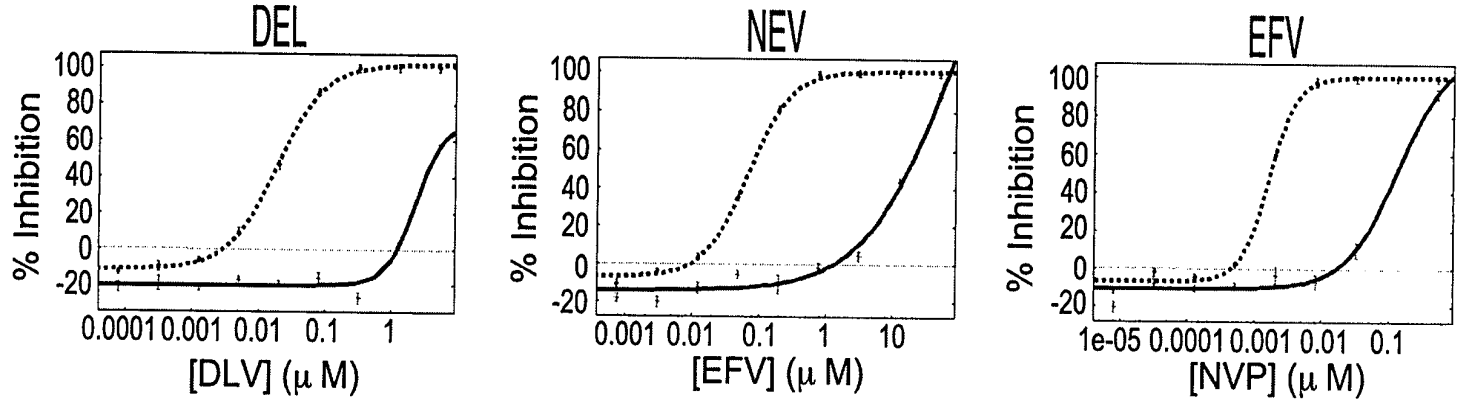


Fig. 12B

Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutants K103N, I135T AND V245T

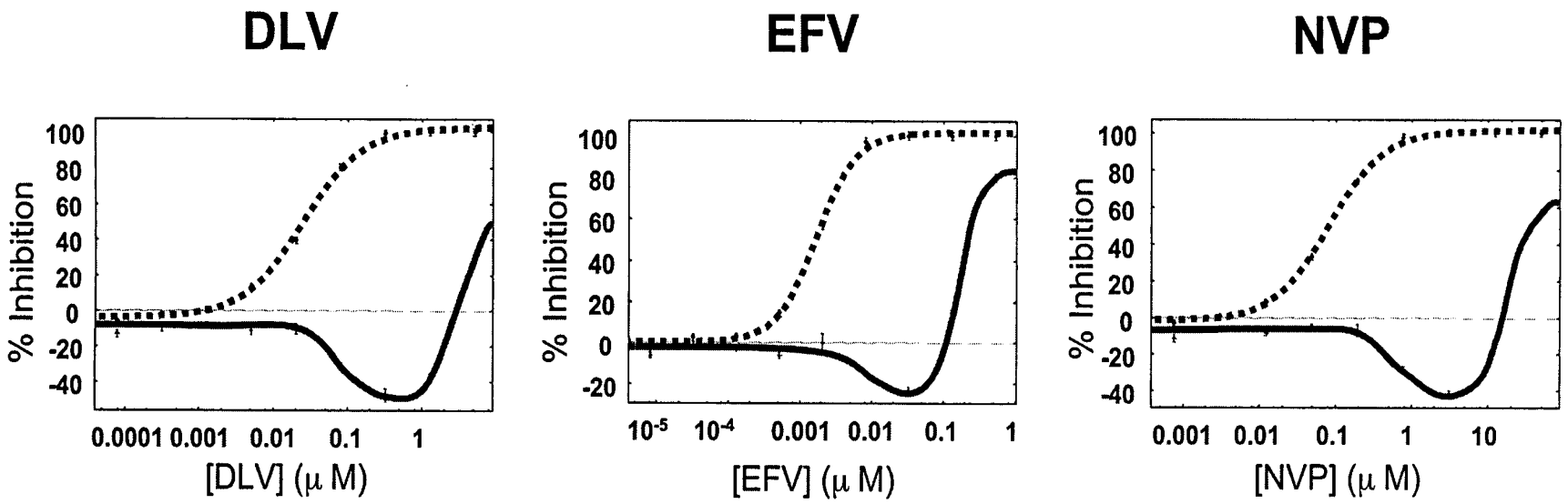


Fig. 13

Patient 13522, reduced susceptibility to NNRTI and drug dependent stimulation of viral replication associated with a mutation at 270 (example 12)

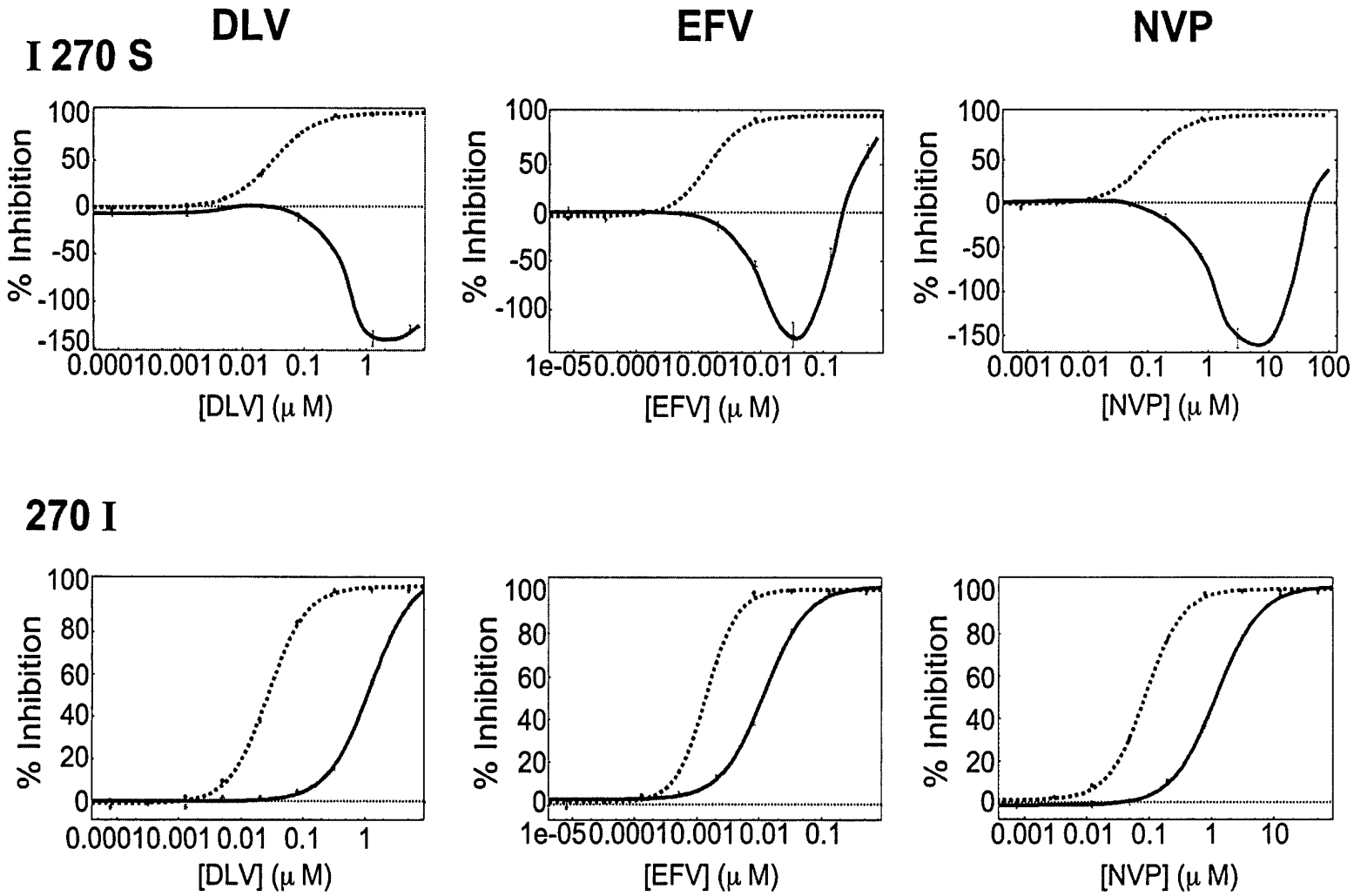


Fig. 14

Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutants I270S

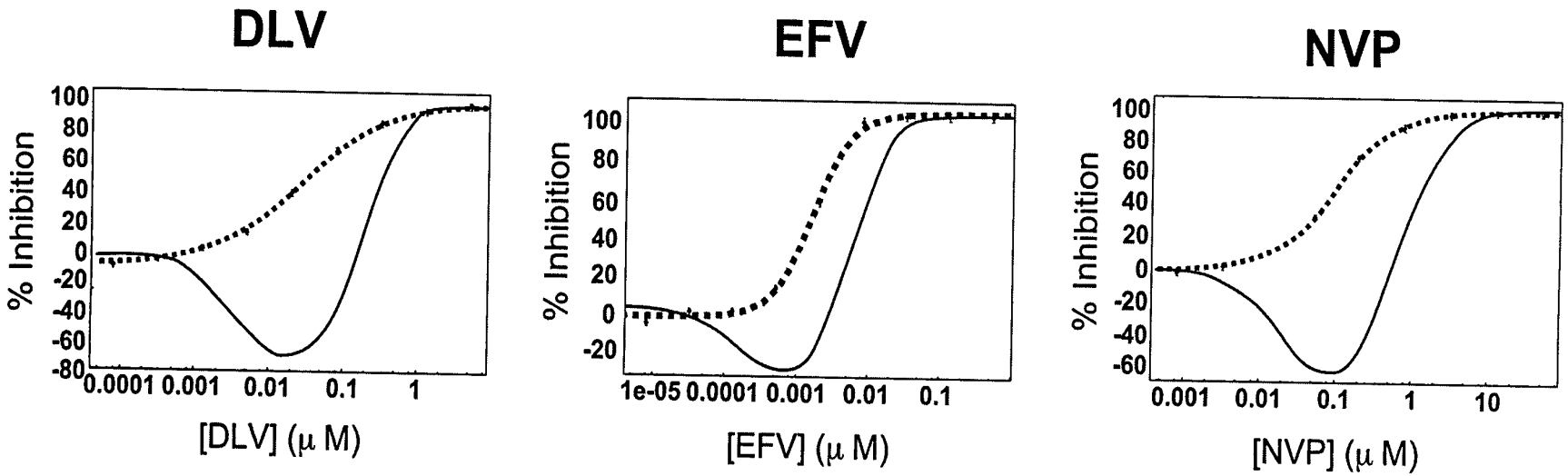


Fig. 15

Clinical History of Patient 1033

Sample ID	Date of Draw	Drug treatment	Duration	Viral load	NVP	DLV	EFV
97-309	09/17/97	AZT, 3TC, IDV	2 yrs.	545000	1.78	0.97	1.03
98-754	09/22/97	"	2 yrs.	801000	1.19	1.16	
	10/03/97	ABC, d4T, NFV, SQV	start	900000			
98-1032	10/10/97	NVP, d4T, NFV, SQV	start	1160000	1.37	0.79	0.93
	10/15/97			2120000			
00-2-011658	11/12/97	"		13300	2.6	1.1	1.4
00-2-011659	11/19/97	"		84500	272	3.1	4.5
	12/03/97			329000			
98-1033	12/29/97	d4T, NFV, SQV	start	1220000	*, dip-250%	13.2, dip--180%	214, dip-170%
99-2-8973	01/28/98	"	12wks	277000	*, dip-180%	18.4, dip-100%	300, dip-150%
98-757	02/26/98	"	16 wks	488000	*, dip-80%	5.2, dip-20%?	16.1, dip-80%
	03/25/98			831000			
99-2-8980	04/22/98	"	24 wks	607000	*, dip-40%	9.3, dip-25%	28, dip-30%
	05/20/98			572000			
	06/17/98			397000			
98-1080	07/15/98	AZT, 3TC, IDV	start	354000	*, dip-45%	2.77, dip-20%	21.86, dip-50%
	08/24/98			100000			
AA1264	12/17/98	"			8.7	0.4	2.5
99-2-6174	05/20/99	"			9.87	0.07	1.59

Fig. 16

Sequences of Reverse Transcriptase of Patient 1033 Virus Samples

Sample ID	RT Sequence
97-309 (9/17/97)	V35I, D67N, T69D, K70R, L109I, M184V, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, L228H, L283I, R284K, V293I, E297K
98-754 (9/22/97)	V35I, D67N, T69D, K70R, L109I, M184V, V189L, T200A, I202T, H208Y, R211K,T215F, D218E, K219Q, H221Y, L228H, L283I, R284K, V293I, E297K
98-1032 (10/10/97)	V35I, D67N, T69D, K70R, L109I, M184V, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, L228H, L283I, R284K, V293I, E297K
00-2-011658 (11/12/97)	V35I, D67N, T69D, K70R, L109L/I/MI, M184V, V189V/L, T200A, I202T, H208H/Y, R211K, T215F, D218E, K219Q, H221H/Y, L228H, L283I, R284K, T286T/A, V293I, E297K
00-2-011659 (11/19/97)	V35I, D67N, T69D, K70R, L109L/I/MI, V179V/I, Y181Y/C, M184M/V, V189V/L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227F/L, L228H, L283I, R284K, T286T/A, V293I, E297K
98-1033 (12/29/97)	V35I, D67N, T69D, K70R, V106A, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L L228H, L283I, R284K, T286A, V293I, E297K
99-2-008973 (1/28/98)	V35I, D67N, T69D, K70R, V106A, Y181Y/C, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L L228H, L283I, R284K, T286A, V293I, E297K
98-757 (2/26/98)	V35I, D67N, T69D, K70R, V106V/A , V108V/I, L109L/V, Y181C, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286A, V293I, E297K
99-2-8980 (4/22/98)	V35I, D67N, T69D, K70R , V108I, L109V, Y181C, D121D/Y, Y181C, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286T/A, V293I, E297K
98-1080 (7/15/98)	(V35I), D67N, T69D, K70R , V108I, L109V, Y181C, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286T/A, V293I, E297K
AA1264 (12/17/98)	V35M/I, D67N, T69D, K70R, V108V/I, L109?, D121D/Y, M184V, V189L, T200A, I202T, H208Y, R211K,T215Y, D218E, K219Q, H221Y, F227F/L, L228H, L283I, H284K, T286A, V293V/I, E297K
99-2-006174 (5/20/99)	V35M, D67N, T69D, K70R, L109I, D121Y, M184V, V189X, T200A, I202T, H208Y, R211K,T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286A, E297K
00-2-011720 (2/14/00)	V35M, D67N, T69D, K70R , V108I, L109V, D121Y, Y181C, V189L, G190A, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286A, V293V/I, E297K

Fig. 17

Patient 014451, reduced susceptibility to NNRTI and drug dependent stimulation of viral replication associated with mutations at 101, 106 and 190 (example 7)

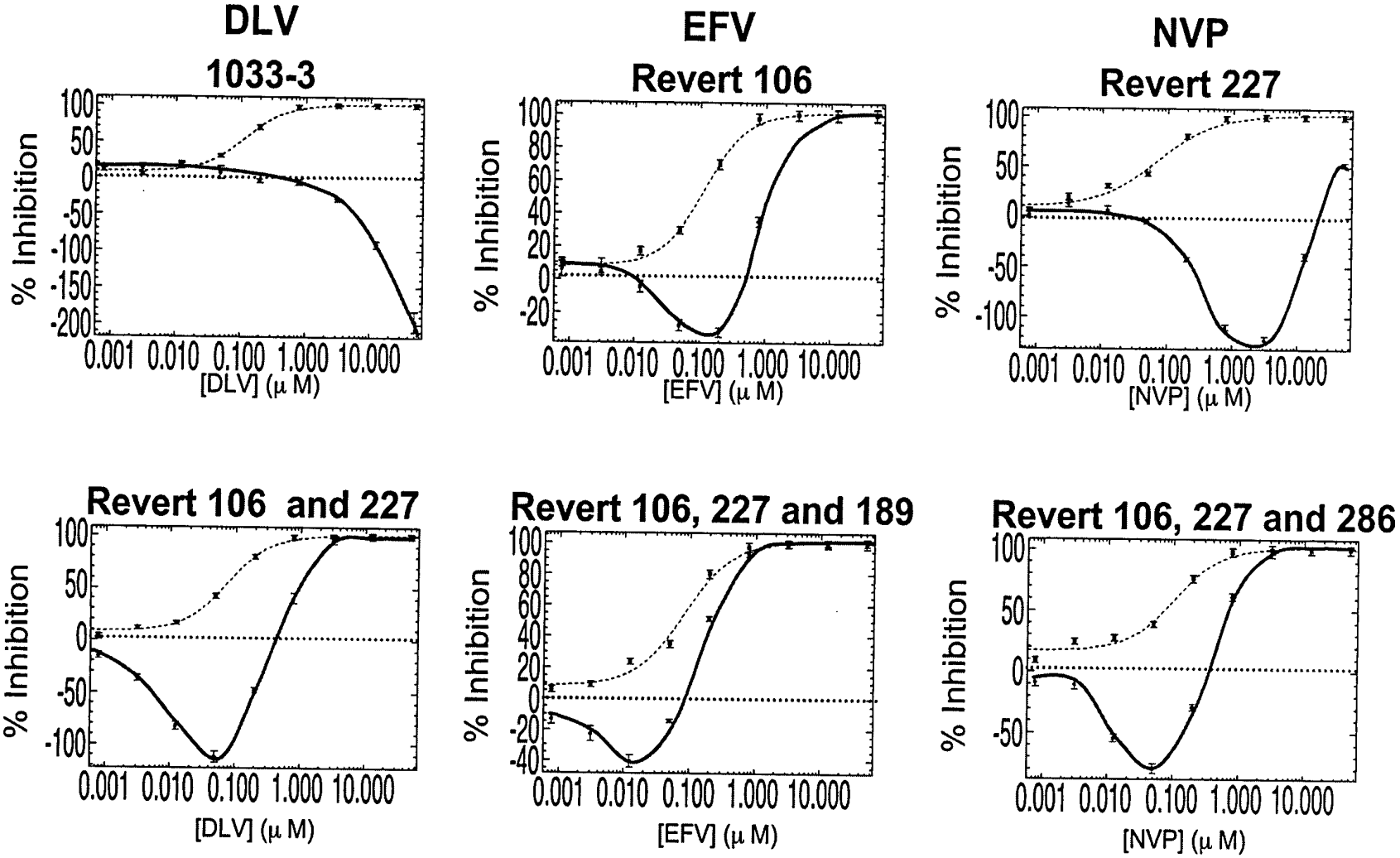


Fig. 18A

Patient 014451, reduced susceptibility to NNRTI and drug dependent stimulation of viral replication associated with mutations at 101, 106 and 190 (example 7), cont.

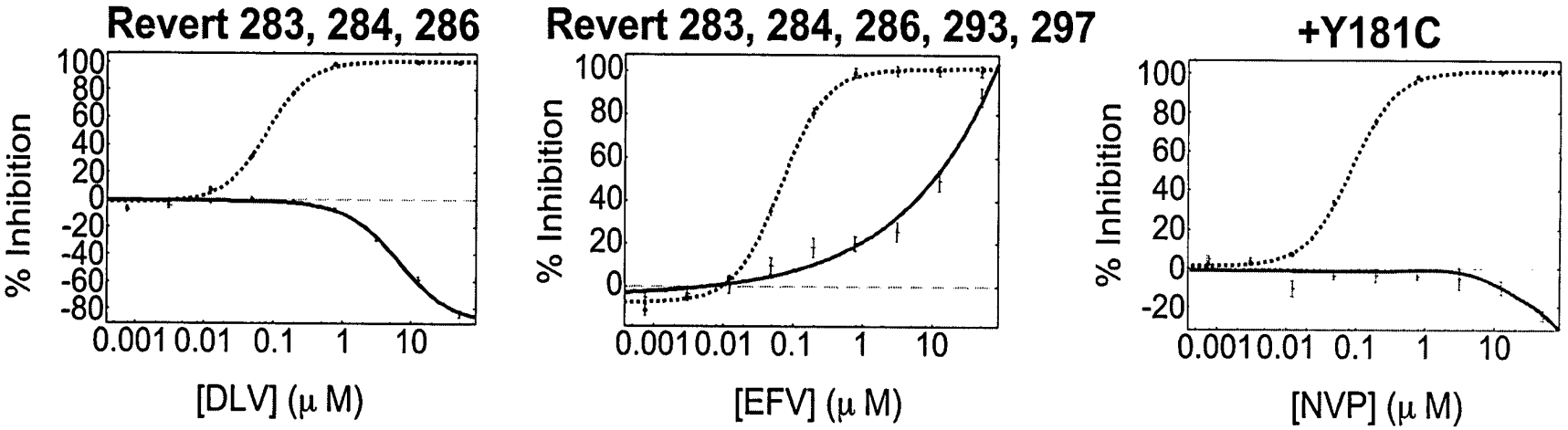
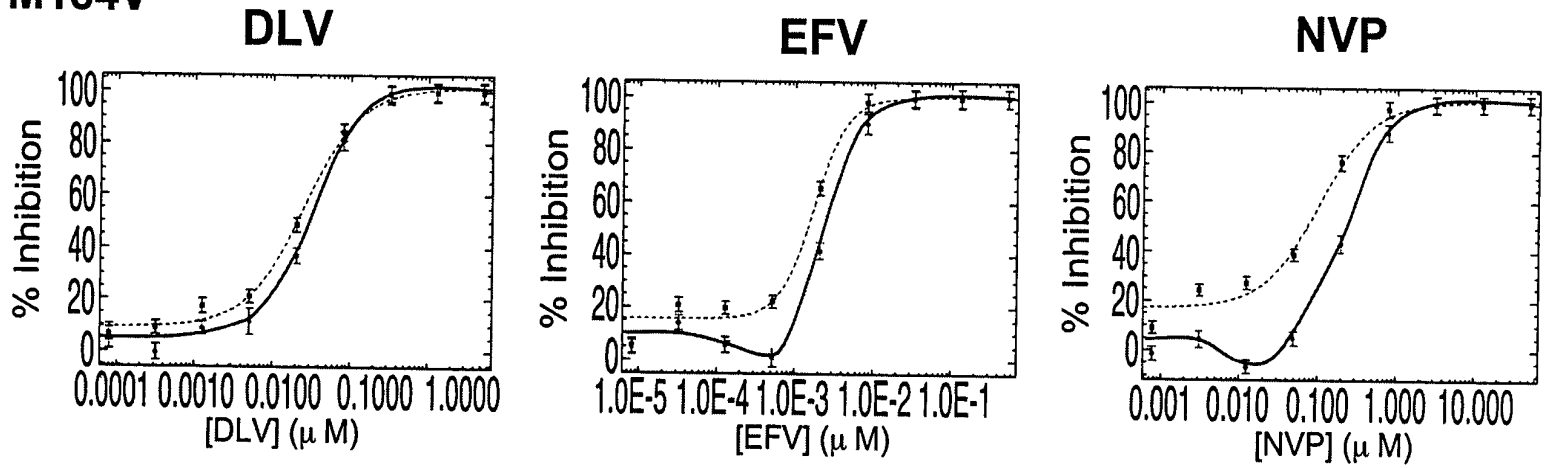


Fig. 18B

Effect of M184V mutation on drug-dependent stimulation of viral replication: RTV-309

M184V



184M

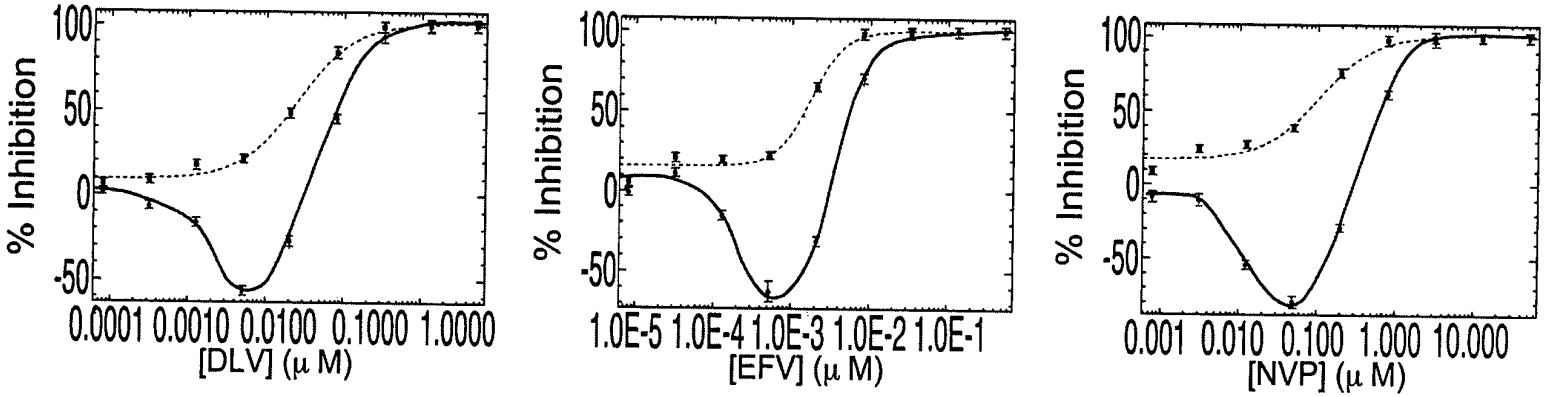


Fig. 19